REMARKS

In response to the examiner's comments, claim 13 is cancelled and "prevention" in claims 44 and 52 has been deleted. The word "prevention" does not appear in claim 53.

We now turn to the rejection of claim 1 under 35 USC 112 that "R^1 and R^2 or R^2 and R^3" together with the atoms to which they are bound form a methylenedioxy group". Since the examiner raised the concern in the July 08, 2008 office action that *"a compound of structure formula I wherein R1 and R2 together are heterocycles having any number of carbon atoms and any number of any of the heteroatoms..."*, a revision has been made in claim 1 as shown in the following

"R^5 and R^6 together may form a 5-7-membered ring;

or R^1 and R^2 together *may form a 5-7-membered* heterocycle;

or R^2 and R^3 together *may form a 5-7-membered* heterocycle; and ...."

Similar modifications have also been made in claims 31 and 60.

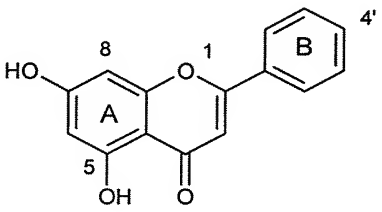
Turning now to the art-based rejection, the compounds in claim 1 are novel and have significant differences from the cited compounds in Cassels' patent for one skilled in the art of flavonoid compounds for the following reasons.

1. Firstly, Cassels' patent discloses a variety of flavone derivatives, focusing on the halogenated chrysin analogs plus some well known flavonoids, in which the 5, 6, 7, 8 and 4' positions are preferably hydrogen, hydroxyl or halo and the most particularly preferred are those wherein the 5 substituent is hydroxyl or hydrogen, the 6-substituent halo, the 7-substituent hydroxyl or halo, the 8- substituent halo and the phenyl group is substituted by hydroxyl and halogen. All of these lack a hydroxyl at the 6 position which is an essential feature of the applicant's claims. Specific named preferred compounds are shown in Figure 1.

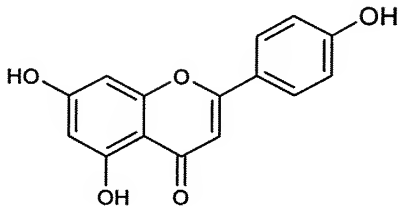
Chrysin (**Compound 1** in Figure 1; the numbering system is also shown) is 5,7-dihydroxy flavone where two hydroxyl groups are on the A ring of the flavone nucleus, while **baicalein** is 5,6,7-trihydroxy flavone (**Compound 6** in Figure 2) where three hydroxyl groups are on A ring.

Apigenin (**Compound 2** in Figure 1) is 4'-hydroxychrysin where two hydroxyls are on the A ring and one hydroxyl is on the B ring.

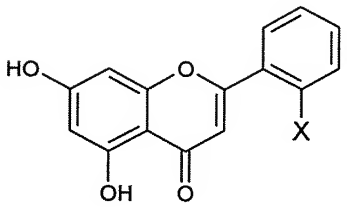
Figure 1.



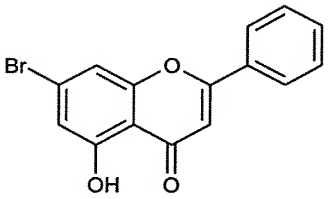
1. Chrysin or 5,7 -dihydroxyflavone (claim 6)



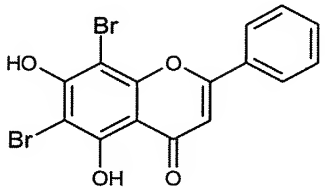
2. Apigenin (claim 8)



3a. 2'-Chlorochrysin (X=Cl)
3b. 2'-Fluorochrysin (X=F); (claim 11)



4. Bromochrysin (claim 15)



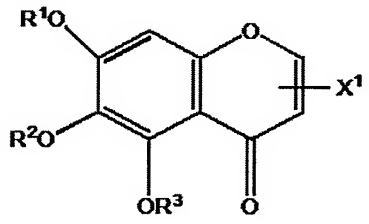
5. 6,8-dibromochrysin (claim 13)

2. Cassels does not covers baicalien analogs, i.e., 5,6,7-trihydroxyflavone analogs (**Compound 6** as shown in Figure 2). All of their compounds lack a hydroxyl at the 6 position which is an essential feature of the applicant's claims. The structure's difference between baicalein and chrysin are three hydroxyls for the former and two hydroxyls for the latter. As a result of the presence of one additional hydroxyl group in this reactive benzo-γ-pyrone ring, chemistry and pharmacology of baicalein (see Background of the Invention of this patent application, p. 1-3) are quite different from chrysin (http://en.wikipedia.org/wiki/Chrysin) and they belong to two distinct chemical classes of compounds, characteristic of flavonoid compounds (see further discussion below in the Section of Additional Support 1.).

3. In addition, Formula I in claim 1 of the present application includes X^1 which is defined as ArX^3 and substituted at either 2 or 3 position of the benzopyrone. ArX^3 distinguishes from the B ring of Cassels' disclosure, which covers only hydroxyl and halogen, in many aspects as shown below:

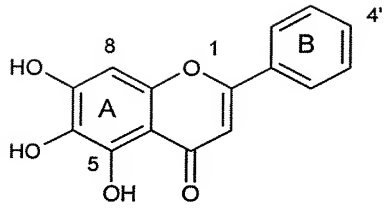
a) Ar of ArX^3, i.e. the B ring, can be furanyl, thienyl, pyridyl, cyclohexyl or benzylas well as phenyl (**Compound 7** is illustrated as one example in Figure 2);

b) X^3 as defined in Formula I is drastically different from simple OH or halogen substituents as defined in Cassels' patent. Some synthesized compounds from claim 1 are also covered in claim 11 as new compounds and structures of a few new compounds such as **Compound 8** (Example 12a, p. 33 lines 28-35 of the application), **Compound 9** (p. 35 lines 32-35), and **Compound 10** (p. 34 lines21-24) are illustrated in Figure 2 to demonstrate that their structures are indeed novel and quite different from those in Cassels' patent as shown in Fig. 1. Furthermore, those novel compounds in claim 11 have already been allowed by the examiner.

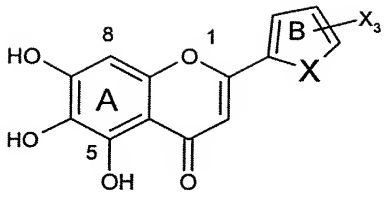


Formula (I)

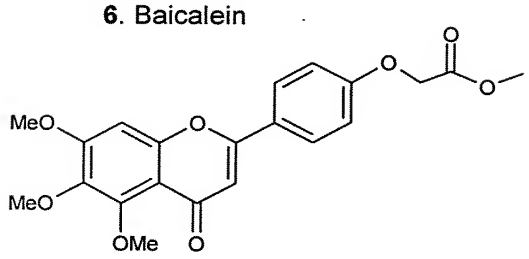
Figure 2



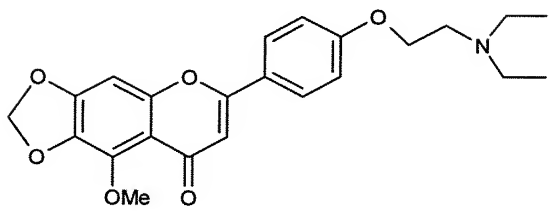
6. Baicalein



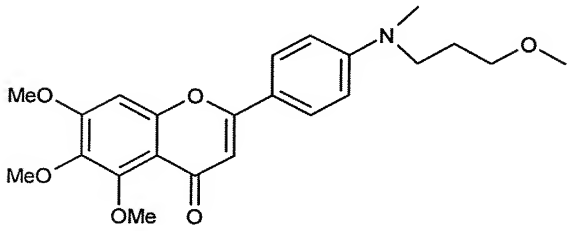
7. X= O or S (claim 1)



8. (claim 1 and 11)



9. (claim 1 and 11)



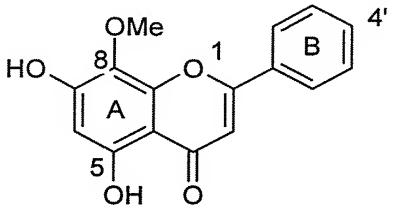
10. (claim 1 and 11)

Additional Support that chrysin analogs by Cassels can not serve as a prior art for baicalein analogs

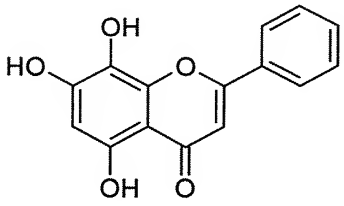
1. Importance of hydroxyl groups in the A ring of the flavone nucleus This discussion is just to demonstrate that the hydroxyl group's number and location will significantly affect Log D and boiling points (see Wikipedia.com) as examples to support that positional isomers or additional hydroxyl group may render the given molecule as a unique class of compound. In organic chemistry and the pharmaceutical sciences, a **distribution coefficient** (D) or Log D is the ratio of the equilibrium concentrations of all species (unionized and ionized) of a molecule in octanol to same species in the water phase at a given temperature, normally 25° C. Log D serves as a measure for lipophilicity of a compound and plays an important role in pharmacology, pharmacodynamics and pharmacokinetics of a drug. As shown in Table 1, Log D for chrysin is 1.67 which is lower or less hydropholic than that of 5,6,7-trihydroxyflavone (baicalein), 1.88, but higher or more hydrophobic than 5,7,8-trihydroxyflavone, (**Compound 12**), 1.01, and Wogonin (**Compound 11**), 1.22. It is

unexpected that chrysin (2 OH groups) would be less hydrophobic than baicalein (with 3 OH groups). Log D for Wogonin is expected to be lower that that of chrysin, as it has 3 OH groups compared to 2 OH groups in chrysin. The boiling points for the four compounds are different, reflecting the effects of relative position of hydroxyl group on the ring. In monohydroxylated flavones, 6-hydroxyflavone is the most hydrophobic compound (Log D = 3.71) which is much higher those of its positional isomers, i.e. 5-, 7- and 8-hydroxyflavone 2.37, 2.79 and 2.52 respectively). Again, this reflects the positional effects on Log D. The boiling points, 425 ^{0}C for 5- and 8-hydroxyflavone are the same and lower than those of 6- and 7-positional isomers. This is because there are intramolecular hydrogen bonding in the 5- and 8-positional isomer (8-hydroxyflavone: forming hydrogen bonding with the ether oxygen of the pyrone; 5-hydroxyflavone: with the carbonyl oxygen of the pyrone which reduces intermolecular force. These two examples, i.e. Log D and boiling points, indicate the simple OH group in the different position of the benzopyrone ring as well as the numbers of OH groups will greatly influence the chemistry and pharmacology of the flavone compound and each positional isomer or compounds with different numbers of OH groups are their own entities.

Figure 3



11. Wogonin



12. 5,6,8-trihydroxyflavone

Table 1. Log D and Boiling Points of Hydroxylated Flavones*

Chemical Name	Log D	Hydrogen Bond Donors/Acceptors	Boiling Point
Baicalein	1.88	5/3	576
5,7,8-Trihydroxyflavone	1.01	5/3	528

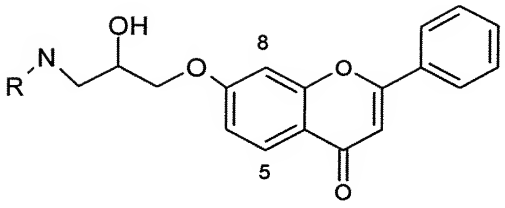
Wogonin	1.22	5/2	518
Chrysin	1.67	4/2	492
5-Hydroxyflavone	2.37	3/1	425
6-Hydroxyflavone	3.71	3/1	450
7-Hydroxyflavone	2.79	3/1	450
8-Hydroxyflavone	2.52	3/1	425

* All data are obtained from from ACD/Labs in ChemSpider.com

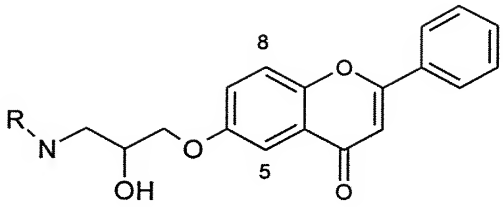
2. Positional Isomers have distinct pharmacological activities and are patentable

1) Flavodilol (R= nPr, **Compound 13 in** Figure 4) is an antihypersive agent which reduces hypertension in hypertensive rats with no beta-blocking activity, while the corresponding 8-isomer (**Compound 15**) is a beta-blocker without antihypertensive activity in rats. The corresponding 6-isomer (**Compound 14**) is a weaker antihypertensive agent without beta-blocking activity, while the 5-isomer (**Compound 16**) is inactive in both activities. (J Med. Chem. 1989, 32, 183-192),

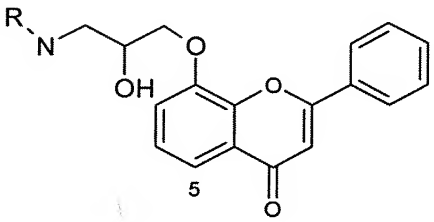
Figure 4



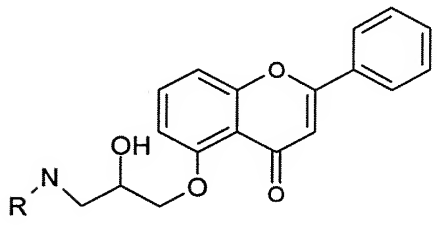
13. Antihypersive with no β-blocking activity



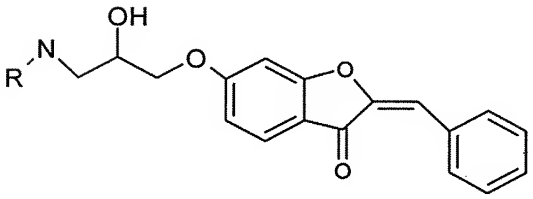
14. Weaker antihypertensive with no β-blocking activity



15. β-blocking activity
No antihypertensive



16. No antihypertensive
No β-blocking activity



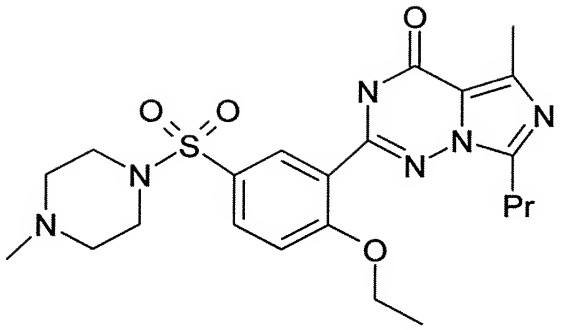
17. Aurone derivative

2) To further illustrate the point, Edwin Wu, one of the inventors in this application did obtain four US patents on antihypertensive chromonoxypropanolamines, i.e. derivatives of chromones including flavones, isoflavones, 2,3-diphenylchromones and aurones (US 4,495,198 Antihypertensive chromonoxypropanolamines; US 4,668,804 Chromones; US 4,668,805 Chromones; US 4,806,660: Aurone oxypropanolamines). All the compounds exhibited antihypertensive activity *in vivo*.

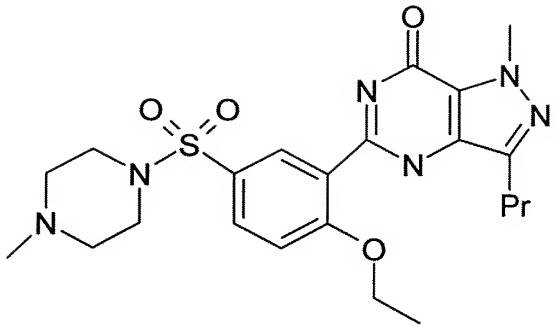
3. PDE5 Inhibitors and Statins

Two patented PDE5 inhibitors (Figure 5) share very similar structures and in fact both are isomers. The difference is that Levitra has an imidazole ring fused to pyrimidone, while Viagara has a pyrazole. Similarly two patented statins (Figure 6) , Zocor and Pravachol, share very similar structures and both are patentable.

Figure 5

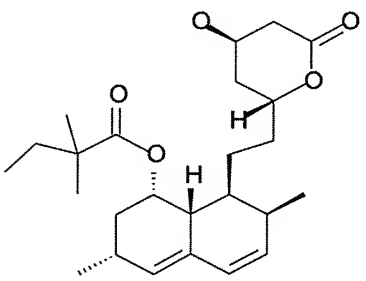


Vardenafil (Levitra)

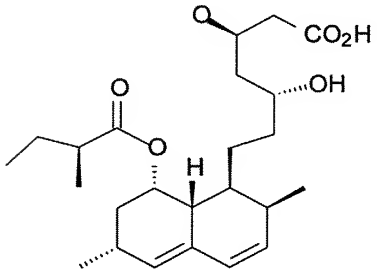


Sildenafil (Viagara)

Figure 6



Simvastatin (Zocor)



Pravastatin (Pravachol)

It is therefore submitted that the claims meet the requirements of 35 USC 102 and 103.

In view of the foregoing, it is submitted that this application is in order for allowance and an early action to this end is respectfully solicited.

Respectfully submitted,

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